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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,507	11/28/2001	Laixin Wang	3302.2.1	3067

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,507	WANG, LAIXIN	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64 and 84-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-17,20-26,28-54,56-64,84-93 and 96* is/are rejected.

7)☒ Claim(s) *18,19,27,35,55,94 and 95* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/19/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/23/05 has been entered.

Claims 65-83 were canceled and claims 84-96 were added as requested.

Claims 1-64 and 84-96 are pending and under consideration in this Office Action.

The elected species of carrier comprising PEI, synthetic or natural polypeptide ligands, streptolysin O, and a polypeptide linker is free of the art, as are claims 18, 19, 27, 30, 35, 55, 56, 94, and 95. The remaining claims are obvious or anticipated for the reasons set forth below.

Claim Objections

Applicant's amendments were sufficient to overcome the previous objections to claims 17, 30, 48, and 56.

Claims 6, 24, and 51 are objected to. The words "at least one" should be inserted between "the" and "targeting moiety". See e.g. claim 44.

Claims 6, 24, 44, and 51 are objected to because --a-- should be inserted immediately before "lectin".

Claim 40 is objected to because the first letter is not capitalized.

Drawings

Applicant has submitted drawings which are accepted for the purpose of examination.

Rejections Withdrawn

All previous art rejections are withdrawn in view of Applicant's amendment requiring a carrier molecule comprising a single biocompatible hydrophilic backbone polymer.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is rejected because it recites "the biodegradable peptide" without antecedent basis.

Claims 55 and 56 are indefinite because it is unclear what is the role of the linker in the method of claim 55. The claims are directed to a method "comprising a linker". It is unclear from this recitation what are the metes and bounds of the claimed methods.

It is suggested, pending a demonstration of support in the specification, that the phrase --wherein one or more of the linkers-- could be substituted for "comprising a linker which."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 89-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 89-92 recite molecular weight ranges of "about 800 to about 2000" Da, "about 800 to about 1200 Da", "about 400 to about 800" Da, and "about 1200 to about 2000" Da. The specification provides no written or exemplary support for these precise ranges, so one of skill in the art could not conclude that Applicant had contemplated these limitations at the time of the invention. As a result they represent new matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-7, 9-17, 20-25, 31-34, 36-44, 48-51, 53, 54, 57-62, 84-93, and 96 are rejected under 35 U.S.C. 102 paragraphs (a) and (e) as being anticipated by Kabanov et al (US Patent 6,221,959).

Kabanov taught complexes of nucleic acids and copolymers, and methods of delivery of the complexes to cells. Copolymers of the structure R-A-R' were disclosed, wherein the R and R' groups are polycations such as polyethyleneimine and the A is a polyether polymer such as polyethylene glycol (PEG). See abstract; column 4, lines 5-11; column 5, lines 42, 43, 62-67 through column 6, line 5; column 7, lines 4-34, especially line 21; column 13, lines 29-46, especially line 38; and column 17, lines 37-45. Kabanov taught the attachment of polypeptide targeting ligands such as antibodies and hormones (see column 19, lines 5-8, 15-25, and 45-51) and lysis agents (see column 19, lines 29-38). Kabanov taught linkers joining the hydrophilic and cationic polymers, including ester and ether linkages (see column 17, line 40). The 'A' groups of Kabanov can consist of 5-400 polyoxyalkylene groups such as PEG, generally having a molecular weight of 30-500 per monomer. See paragraph bridging columns 12 and 13, and column 13, lines 12-16. The polycationic polymers R will also generally have a

molecular weight of 30-500 per monomer and be present at between 5-200 monomers per polymer.

Thus Kabanov anticipates the claims.

Claims 1, 4-6, 9-14, 31, 32, 36, 38, 39, 41, 43, 44, 48, 50, 51, 53, 54, 57, and 58, are rejected under 35 U.S.C. 102 paragraphs (a) and (e) as being anticipated by Wagner et al (US Published Patent Application 2001/0005717), as evidenced by GenBank Accession No. AAP45055 (5/6/2003).

Wagner taught methods of delivering nucleic acids to cells by forming complexes with a PEI carrier, wherein the PEI is covalently modified by PEG, which is covalently modified with transferrin. In terms of the instant invention, Wagner's PEI is considered to be a hydrophilic polymer, the PEG molecules are considered to be linkers, and transferrin is considered to be a polycation in view of the evidence of GenBank Accession No. AAP45055 which disclosed the sequence of trasferrin which contains 99 positively charged amino acid residues. See page 11 of this Action. Wagner taught that the PEG used should be from 500-20,000 D or, assuming a monomer molecular weight of 59 Da and 3 main chain atoms per monomer, about 27-1017 atoms in length. See paragraphs 25 and 26. The PEI used has a molecular weight from 700 Da to 2,000,000 Da, with specific examples of 1300, 2000, and 25000 Da. See paragraph 22.

Thus Wagner anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 7, 8, 17, 25, 26, 31, 45, 48, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kabanov et al (US Patent 6,221,959) in view of Bayley et al (US Patent 5,777,078)

Kabanov taught complexes of nucleic acids and copolymers, and methods of delivery of the complexes to cells. Copolymers of the structure R-A-R' were disclosed, wherein the R and R' groups are polycations such as polyethyleneimine and the A is a polyether polymer such as polyethylene glycol (PEG). See abstract; column 4, lines 5-11; column 5, lines 42, 43, 62-67 through column 6, line 5; column 7, lines 4-34, especially line 21; column 13, lines 29-46, especially line 38; and column 17, lines 37-45. Kabanov taught the attachment of polypeptide targeting ligands such as antibodies and hormones (see column 19, lines 5-8, 15-25, and 45-51) and lysis agents (see column 19, lines 29-38). Kabanov taught linkers joining the hydrophilic and cationic polymers, including ester and ether linkages (see column 17, line 40). The 'A' groups of Kabanov can consist of 5-400 polyoxyalkylene groups such as PEG, generally having a molecular weight of 30-500 per monomer. See paragraph bridging columns 12 and 13, and column 13, lines 12-16. The polycationic polymers R will also generally have a

molecular weight of 30-500 per monomer and be present at between 5-200 monomers per polymer.

Kabanov did not teach the use of streptolysin O as a lysis agent.

Bayley taught compositions for improving DNA uptake into cells, comprising a streptolysin O attached to a targeting ligand. See column 1, lines 47-59 and column 2, lines 13-21.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use streptolysin O in the invention of Schacht. One would have been motivated to do so because Bayley teaches that streptolysin O is useful for forming pores in membranes to allow delivery of nucleic acids, such that one would have reasonably expected to improve delivery efficiency. Note that Kabanov contemplates incorporating into the complexes any molecule that enhances transport or accumulation of nucleic acids into cells. See column 19, lines 10-15.

Thus the invention as a whole was prima facie obvious.

Claims 1, 28, 29, 31, 46-48, 63, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al (US Published Patent Application 2001/0005717) in view of Kircheis et al (Gene Therapy 4: 409-418, 1997).

Wagner taught methods of delivering nucleic acids to cells by forming complexes with a PEI carrier, wherein the PEI is covalently modified by PEG, which is covalently modified with transferrin. See abstract; and paragraph 32. In terms of the instant invention, Wagner's PEI is considered to be a hydrophilic polymer, the PEG molecules

are considered to be linkers, and transferrin is considered to be a polycation. Evidence that transferrin is a polycation comes from Uzan who disclosed its sequence containing 44 positively charged amino acid residues.

Wagner did not teach a complex comprising a single PEI molecule with about 4 to about 100, or about 8 to 15, polycationic polymers attached to it by linkers. However, Wagner did teach PEI directly modified with different amounts of transferrin (polycation), i.e. PEI comprising 2 or 4 transferrins per PEI molecule. See e.g. Fig. 8.

Kircheis taught DNA/PEI complexes comprising 2, 4, or 8 transferrins per PEI, and showed that transfection efficiency varied with the amount of transferrin conjugated to PEI. (Note that the compositions of Kircheis contain no linker, so Kircheis is not a 102 reference.)

It would have been obvious to one of ordinary skill in the art at the time of the invention to conjugate transferrin molecules to PEG molecules in PEI/PEG conjugates in the range of 4-100, or 8-15, transferrins per PEI. One would have been motivated to do so because Kircheis exemplified the use of 4-8 transferrins, and Wagner taught that positioning the transferrin at the end of a PEG linker allows better access to the receptor. See paragraph 32.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Claims 18, 19, 27, 30, 35, 55, 56, 94, and 95 are free of the prior art of record. Claims 18, 19, 27, 35, 55, 94, and 95 are objected to as depending from a rejected claim, but would be allowable if rewritten in independent form incorporating all of the limitations of the claims from which they depend.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.